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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional)	
0010872.0556916	

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on _____

Signature _____

Typed or printed name _____

Application Number	Filed
10/801,517	March 16, 2004
First Named Inventor	
Xiaoyang Qi	
Art Unit	**Examiner**
1643	Sang, Hong

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

- ☐ applicant/inventor.
- ☐ assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)
- ☑ attorney or agent of record. Registration number 41,487.
- ☐ attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34 _____

Signature

Stephen R. Albainy-Jenei
Typed or printed name

(513) 651-6839
Telephone number

December 10, 2009
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of _____ forms are submitted.

This collection of information is required by 35 U.S.C. 132. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11, 1.14 and 41.6. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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IN THE UNITED STATES PATENT & TRADEMARK OFFICE

Applicant:	Xiaoyang Qi	: Paper No:	
Serial No.	10/801,517	: Group Art Unit:	1643
Filed:	March 16, 2004	: Examiner:	Sang, Hong

For: SAPOSIN C-DOPS: A NOVEL ANTI-TUMOR AGENT

ARGUMENTS IN SUPPORT OF
PRE-APPEAL BRIEF REQUEST FOR REVIEW
In accordance with 1296 Off. Gaz. Pat. Office 67 (July 12, 2005)

Confirmation No. 4062

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Applicants respectfully assert that the Office Action makes legally incorrect rejections under 35 U.S.C. 112 and fails to make out a *prima facie* case of obviousness for any of those claims. Therefore, the applicant requests that the panel withdraw the Office Action's rejections, and allow the claims in their present form. The concise arguments for which review is requested are set forth below.

Claim Rejections - 35 USC § 112, 1st paragraph (Written Description)

The Examiner has maintained the rejection of claims 1-8 and 50-57 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The Examiner contends that the specification does not provide adequate written description regarding which amino acids and how many of them can be changed in the wild type saposin C such that the resulting variants still have the anti-tumor activity.

Unlike the claims presented in the decision in *Ex parte Porro*, in which the Board of Patent Appeals and Interferences affirmed the Examiner's determination that claims to a method of making ascorbic acid (vitamin C) lacked an adequate written description, the present claims are already self-selected for the active structure. The relevant structure is an

80 amino acid fragment taken from the 524 amino acids present in a prosaposin polypeptide of the invention. The structure in this case is the sequence itself. However, that does not mean there cannot be some variation in that structure. Biologists have recognized for over forty years that most variation in most proteins is neutral, even when it has structural consequences like changing a protein's pI. Proteins, in short, are not so fragile.

The saposin fold comprises five alpha-helices (H1 through H5), which are responsible for proper orientation within the phospholipid bilayer of the nanovesicles and further comprise the enzyme activation of domain of amino acids 48-62, which span helices H3 and H4. The consensus sequence is described (Qi et al 1996) and the level of conservation here is very high, with 6 conserved, 7 fairly conserved. Known amino acid variations found within this region include V51L, D52G, D52V, Y54F, S56P, S56D, S56R, I58L, I58T, L59V, S60D, S60A, I61V, I61L and L62F.

As noted by the Office, satisfactory disclosure "depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed."[1] The Office is reminded that "[d]escription of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces."[2]

The prior art and the previous 1.132 Declarations[3] show that the five alpha-helices (H1 through H5) are required for the function of retaining not just plasma membrane affinity but an anti-tumor activity as well. The specification establishes a correlation between the 80-amino acid saposin C peptide structure and the plasma membrane affinity and anti-tumor activities. In addition, it is well within the capability of one of ordinary skill in the art, through routine laboratory procedures, to ascertain whether or not a given polypeptide retains plasma-membrane affinity and whether or not a given nanovesicle exhibits anti-tumor activity.

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[1] *Office Action, p.5, citing Revised Guidelines for the Written Description Requirement.*
[2] *MPEP* § 2163.
[3] 1.132 Declarations of Qi submitted 3/03/08 and 10/31/08.

It is well known in the art that the proteins of the invention may be altered in various ways including the amino acid substitutions, deletions, truncations, and insertions. Based on the description in the present application together with what is known in the art, the description provides adequate guidance as to which amino acids are highly conserved and, thus, likely to be necessary versus those that are more variable. Therefore, those of ordinary skill in the art would be able to envision the detailed structures of the encompassed variants regarding which amino acids and how many of them can be changed in the wild type saposin C such that the resulting variants still have the anti-tumor activity. Applicants respectfully assert that the disclosure of sequences and domain sites further provides meaningful, specific guidance that would allow one of ordinary skill in the art to "immediately envisage" the claimed invention.

Claim Rejections - 35 USC § 112, 1st paragraph (Enablement)

The Examiner has maintained the rejection of claims 1 -8, and 50-57 under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for a nanovesicle comprising a polypeptide having an amino acid sequence at least 95% identical to SEQ ID NO:2, or a polypeptide of SEQ ID NO:2 having one or more conservative substitutions. The Examiner contends that it would require undue experimentation to perform the invention as claimed.

In contrast to the conclusions of the Office Action, the specification provides sufficient guidance to make and identify the polypeptide molecules encompassed by the claims. Methods for sequence alignments, sequence comparisons, and determining percent sequence identity are within the knowledge of one of ordinary skill in the art. Methods for assaying whether the nucleotide sequences encode proteins that retain plasma membrane binding are known in the art and are also provided in the specification in working examples.[4]

The Federal Circuit has repeatedly stated that enablement is not precluded by the necessity for experimentation, so long as the experimentation needed to practice the invention is not *undue*.[5] "That some experimentation is necessary does not preclude enablement; the amount

[4] See 1.132 Declarations of Qi submitted 3/03/08 and 10/31/08.
[5] *In re Wands* U.S.P.Q. 2d 1400 (Fed. Cir. 1988).

of experimentation, however, must not be unduly extensive."[6] Furthermore, a considerable amount of experimentation is permissible, if it is merely routine, or if the specification provides a reasonable amount of guidance in which the experimentation should proceed.[7] A patent claim complies with the enabling requirements if experimentation is necessary so long as such experimentation is reasonable to one skilled in the art.[8] That is the case here.

In the present case, the quantity of experimentation required to practice the invention amounts to two steps: identifying a polypeptide comprising an amino acid sequence having at least 95% identity to SEQ ID NO: 2, and then assaying phospholipid nanovesicles incorporating the polypeptide for functional activity. Thus, ample guidance is provided to allow one of skill in the art to identify additional nucleotide sequences encompassed by the claims. Accordingly, Applicants submit that claims 1-8 and 50-57 are enabled under 35 U.S.C. §112, first paragraph.

Claim Rejections - 35 USC §103

The Examiner has rejected claims 1-8 and 50-57 under 35 U.S.C. 103(a) as being unpatentable over O'Brien (US 5,700,909, Date of Patent: 12/23/1997), in view of Liu et al. (WO 98/33482, Pub. date: 8/6/1998), and Habberfield (US 2002/0099001A1, Pub Date: 7/25/2002, earlier effective filing date 2/1/1995). Applicants assert that there would have been no reason or motivation to combine the cited references and that, even if one did combine the references, they would not teach the claimed invention since a lipid/saposin vesicle formed by the methods described in these references will not function the same and will not exhibit anti-tumor activity as with the vesicles of the present invention.[9]

The O'Brien reference teaches that peptides derived from Saposin C can be used to treat demyelination disorders while the present application describes that the combination of Saposin C and DOPS is necessary for the anti-cancer activity. Saposin C or its peptides alone have no killing effect on cancer cells. While O'Brien discloses that prosaposin or fragment thereof may be advantageously enclosed in a liposome-like (lamellar) structure, peptides delivered this way

[6] *See generally* In re Goodman, 11 F.3d 1046.
[7] *In re Wands*.
[8] *See* Enzo Biochem Inc. v. Calgene, 188 F.3d 1362 (Fed. Cir.1999)
[9] See 1.132 Declarations of Qi submitted 3/03/08 and 10/31/08.

only show use for nerve cell proliferation to counteract degeneration. In the present invention, SapC-DOPS, the lipid and protein freely combine to form nanovesicles. SapC is all across the membrane and not encapsulated. A lipid/saposin vesicle formed by the method of O'Brien will not exhibit anti-tumor activity as with the vesicles of the present invention. The composition of the present invention comprises a SapC-DOPS nanovesicle complex and that it would be clear to one skilled in the art from the description of the present invention within the specification, especially as described in Example 2, that the composition comprises a SapC-DOPS nanovesicle complex and not a mixture of nanovesicles and SapC as described in the above references.

The examiner listed patents by Habberfield and Liu et al. for teaching liposomes composed of PS for drug delivery. As described above, anti-cancer effect requires both composition of DOPS and Saposin C. For example, replacement of DOPS with DOPC does not kill cancer cells while encapsulation of Saposin C in DOPS vesicle for delivery does not kill cancer cells. The results achieved in the present application are unexpected in light of the cited references. Therefore, the applicants request that the panel withdraw those rejections and either allow the pending claims in their current form or re-open prosecution on the merits.

The applicants note that due to the length and content restrictions of the pre-appeal review program, this paper does not include all arguments related to the pending claims. To the extent that applicants have not addressed certain aspects of the present rejection, please do not construe the same as an admission as to the merits of the rejections. Indeed, applicants reserve all rights with respect to arguments not explicitly raised herein.

Respectfully submitted,
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